PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-316WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/05994	International filing date *(day/month/year)* 15.12.2003	Priority date *(day/month/year)* 16.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C51/16		
Applicant RANBAXY LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.07.2004	11.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mercey, J Telephone No. +49 89 2399-8956

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/05994

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-6 as originally filed

Claims, Numbers

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) There is an error in the structural formula (I) in Claims 1, 6 and 19 and on page 1 of the description, said formulae including an erroneous CH_2 group adjacent to the COOH group. This opinion is based on the correct structure.

2) Claim 6 comprises all the features of Claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT). In addition, it would appear essential to the invention that the organic solvent is added "after the oxidation reaction is complete" (cf. page 5, lines 1-2), the current wording embracing the addition of the organic solvent **during** the oxidation, the aim of the present invention apparently being to avoid just this (cf. page 2, lines 15-17).

D1 : WO-A-9500480
D2 : US-A-4254129

NOVELTY (Article 33(2) PCT)

3.1) D1 discloses a process for the preparation of an acid of the present formula I by oxidation of an alcohol of the present formula III (cf. Scheme I on page 129, step d_5 on page 135, lines 13-16 which refers back to step d_2 on page 133, line 28 to page 134, line 12, and Exs. 40 & 41), the oxidation agents referred to on pages 133-134 being potassium permanganate, nitric acid, chromium (IV) oxide, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate and xenic acid. More particularly Ex. 41C teaches the treatment of the alcohol of present formula III with potassium permanganate, water, acetic acid and phosphoric acid. Water is then added and the reaction mixture is worked up. D1 also describes a process for preparing fexofenadine comprising hydrolysing an ester of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid to the corresponding ester of 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid (cf.

Ex. 11), condensing with azacyclonol (cf. Exs. 43-44) and reduction of the product (cf. Ex. 45).

3.2) The process of present Claim 1 differs from that of D1 in that the alcohol III is treated with a hydroxide of an alkali metal, in addition to adding an oxidising agent followed by aqueous acidic work up. Claims 2-18 are novel for similar reasons.

3.3) With regard to Claim 19, the wording "prepared by the process of claim 1 or 6" has no limiting effect on the claim. The process of present Claim 19 is novel over D1, since it involves the hydrolysis of the acetic acid derivative of formula I, whereas in D1 an acetic acid ester is hydrolysed.

3.4) The subject-matter of Claim 20 is not new, since D2 (cf. Claims 8 and 11) describes a method of treating allergic reactions in patients comprising administering to said patient fexofenadine or a pharmaceutically acceptable salt thereof, hydrochlorides being mentioned at D2, col. 3, lines 27-32. The wording "prepared by the process of claim 19" has no limiting effect on the claim, i.e. the subject-matter thereof is the same as any such method of treatment comprising administering fexofenadine hydrochloride prepared by a different process.

INVENTIVE STEP (Article 33(3) PCT)

4) The subject-matter of Claims 1-19 does not involve an inventive step.

4.1) In the light of D1, the problem to be solved by the present invention may be regarded as the provision of an improved process for the preparation of the acid I from the alcohol III, more particularly a process "which does not require the use of any organic solvent during oxidation, rather uses water" (cf. present description, page 2, lines 15-17).

4.2) The solution provided by the process of Claim 1 comprises treating the alcohol III with a hydroxide of an alkali metal, and adding oxidising agent followed by aqueous acidic work up.

4.3) However, it is not seen how this process solves the problem, it not being apparent what is the **effect** of adding the alkali metal hydroxide. If a known process is modified by adding a feature which has no technical function, this modification can not contribute to inventive step, even if the skilled person would never think of such a modification. According to page 4, lines 7-11 of the description, the

hydroxide may be used in the form of a solution in, for example, lower alkanols and ketones, namely organic solvents. In such a case, the oxidation would then inevitably be carried out in the presence of an organic solvent. Claim 1 does not specify that the hydroxide is added in aqueous solution (Claim 1 thus being completely silent regarding the presence of water during the oxidation), nor does Claim 1 exclude the presence of organic solvents during the oxidation. Furthermore, it is not at present apparent what is the advantage of the present process over that of Ex. 41C of D1.

4.4) Dependent Claims 2-5, "independent" Claim 6 (cf. item 2 above), and dependent Claims 7-18 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

4.5) The process of Claim 19 is not inventive, since such a process is analogous to those known in the literature as acknowledged in the application itself (cf. page 5, lines 24-28), D1 describing a process for preparing fexofenadine comprising hydrolysing an ester of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid to the corresponding ester of 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid (cf. Ex. 11), condensing with azacyclonol (cf. Exs. 43-44) and reduction of the product (cf. Ex. 45).

INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

5) For the assessment of the present Claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.